

REMARKS

This Response is to the Office Action, dated August 12, 2010 ("Office Action"). Claims 1, 3-4, and 11-12 are pending; claims 5, 7-8, 13, and 15-19 having been cancelled by virtue of the present amendment. It is respectfully submitted that the application is in condition for allowance. No new matter has been added. Allowance and reconsideration of the application in view of the ensuing remarks are respectfully requested.

The Examiner objects to Applicants' Information Disclosure Statement (IDS) filed July 22, 2010. The foreign prosecution documents listed in the July 22, 2010, IDS were submitted by Applicants in the abundance of caution to disclose material that the Examiner might consider to be relevant to the patentability of the claims. All items cited within the foreign prosecution documents themselves have been previously submitted in Applicants' IDS filings of October 27, 2006 and November 15, 2006 and are part of the Image File Wrapper for this application. The Examiner notes that the search report documents have been considered but lined through all the disclosed documents in the signed PTO form and noted that the lined through documents are not considered. Applicants request that the Examiner initial each of the documents disclosed in the July 22, 2010, IDS as being considered and return the initialed form.

Claims 15-19 remain rejected under 35 U.S.C. §101 as allegedly being directed to non-statutory subject matter for reasons of record. While Applicants do not concede to the merits of the Examiner's rejection, claims 15-19 have been cancelled. Thus, this rejection is moot. Applicants reserve the right to pursue the subject matter of these claims in one or more continuing applications.

Claims 5, 8, 13, 15, and 17-19 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Scherman *et al.* (U.S. Patent 5,945,400) for reasons of record. While Applicants do not concede to the merits of the Examiner's rejection, claims 5, 8, 13, 15, and 17-19 have been cancelled. Thus, this rejection is moot. Applicants reserve the right to pursue the subject matter of these claims in one or more continuing applications.

Claims 5, 7-8, 13 and 15-19 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Colley *et al.* (WO 99/53943) as evidenced by Robbins *et al.* (Trends Biotechnol. 16 (1):35-40, 1998). While Applicants do not concede to the merits of the Examiner's rejection, claims 5, 7-8, 13 and 15-19 have been cancelled. Thus, this rejection is moot. Applicants reserve the right to pursue the subject matter of these claims in one or more continuing applications.

Claims 1 and 11 remain rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Havemann *et al.* in view of Souttou *et al.* and Powers *et al.* for reasons of record. The Examiner asserts that one of ordinary skill in the art could, upon reading Havemann *et al.*, Souttou *et al.*, and Powers *et al.*, reasonably conclude that pleiotrophin (PTN) may be used for inducing differentiation of monocytic cells to endothelial cells. Applicants respectfully traverse the rejection.

Havemann *et al.* Does Not Contain an Enabling Disclosure of the Use of PTN as the Growth Factor that Promotes the Differentiation of Mononuclear Cells Into Endothelial Cells

The Examiner insists that Havemann *et al.* has an enabling disclosure that PTN is a growth factor that promotes the differentiation of mononuclear cells into endothelial cells and cites paragraphs 0066 and 0072.

Havemann *et al.* discloses the use of culture conditions, including **one or more** growth factors, to influence differentiation, survival, migration or vascularization. The laundry list of growth factors provides one of ordinary skill in the art a pool to draw a myriad of possible combinations of growth factors to influence differentiation, survival, migration or vascularization. To determine which combination(s) of growth factors will induce transdifferentiation of the mononuclear cells into endothelial cells will require undue experimentation. To just focus on growth factors, the list includes at least 35 growth factors (when items such as KDR and Flt ligands are each counted as one for simplicity, rather than more than one). To determine which **growth factor or combination of growth factors** can be responsible for transdifferentiating a monocytic cell into an endothelial cell is **not** simply having 35 cultures to test each growth factor as the Examiner is alleging. The formula for determining the number of possible combinations of 35 growth factors is **2ⁿ-1**. This formula was obtained as

follows and is a matter of mathematics. The number of k-combinations for all k is:

$$\sum_{0 \leq k \leq n} \binom{n}{k} = 2^n$$

, where k is the number of items in a combination and n is the total number of items from which the combination can be selected. In this instance, “n” is 35; and “k” (number of items in a combination) can be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34 or 35; each “k” results in a certain number of possible combinations, and thus, a sum of all “k” is taken. One is subtracted from 2^n

$$\sum_{0 \leq k \leq n} \binom{n}{k} = 2^n$$

because the formula, $\sum_{0 \leq k \leq n} \binom{n}{k} = 2^n$, accounts for the “combination” where nothing is selected (i.e., k = 0). However, Havemann *et al.* discloses that **one or more** growth factors are selected. Thus, we subtract the possibility where no growth factor is selected.

Applying this to the present case, the number of possible combinations for **one or more** of 35 growth factors would be $2^{35}-1$, which is **34,359,738,367 possible combinations**. No guidance was given that would direct one of ordinary skill in the art to use PTN and thus, undue experimentation will be required to determine which combination(s) of growth factor(s) will transdifferentiate a monocytic cell into an endothelial cell. Clearly, Havemann *et al.*’s disclosure of the list of growth factors is not an enabling disclosure that PTN is responsible for transdifferentiating a monocytic cell into an endothelial cell.

Furthermore, Applicants provided the Natarajan Declaration as evidence to show that one of ordinary skill in the art would not find that Havemann *et al.* teaches one of ordinary skill in the art to use PTN to differentiate monocytes into endothelial cells. The Examiner must consider this as evidence that Havemann *et al.* does not have the enabling disclosure that the Examiner alleges.

The Examiner Must Give Meaningful Consideration of the Natarajan Declaration

The Examiner asserts that the Natarajan Declaration filed with Applicants’ previous response is insufficient to overcome the rejections of record because, “while Applicant expresses statement regarding the underlying basis of Applicant’s opinion and interpretation of the prior art, particularly Havemann *et al.*, Applicant’s opinion on the ultimate legal issue is not evidence, and Applicant has not provided factual support for the stated opinions.”

It has long been understood that “[E]vidence rising out of the so-called ‘secondary considerations’ must always when present be considered en route to a determination of obviousness.” *Stratoflex, Inc. v. Aeroquip Corp.*, 713, F.2d 1530, 1538, 218 U.S.P.Q. 871, 879 (Fed. Cir. 1983). On the specific issue of evidence in the form of a CFR 1.132 declaration, the Federal Circuit has clearly stated that “When a patent applicant puts forth rebuttal evidence, the Board must consider that evidence.” *In re Sullivan*, 498 F.3d 1345, 1354 84 U.S.P.Q.2D (BNA) 1034, 1043 (Fed. Cir. 2006). In *Sullivan*, the Federal Circuit held that a BPAI decision affirming an Examiner’s §103 rejection was erroneous for failure to consider the applicant’s submission of three separate 1.132 declarations evidencing expectations of failure for those of skill in the art. Moreover, MPEP §716.01(B) also requires that “[e]vidence... must be considered by the Examiner whenever present,” and if not found to be persuasive, at least provide specific explanation of its insufficiency as evidence. In sum, there is a strong mandate for the PTO to consider rebuttal evidence attempting to traverse a §103 obviousness rejection.

Whether a CFR 1.132 Declaration qualifies as evidence and its level of probative value depends on its content. At one end of the spectrum, presentation of facts (e.g., test results, sales figures) are evidence and given greater probative value. MPEP §716.01(c) I. On the opposite end of the spectrum, arguments of counsel are not evidence. MPEP §716.01(c) II (citing *In re Schulze*, 346 F.2d 600, 602, 145 U.S.P.Q. 716, 718 (CCPA 1965)). Likewise, opinions purely on an ultimate legal issue are generally not considered evidence. *In re Chilowsky*, 306 F.2d 908, 134 U.S.P.Q. 515 (1962) (expert opinions that application meets 35 U.S.C. §112 requirement not entitled to any evidentiary weight). Case law places other types of expert opinions in-between the two extremes, with factually-supported opinions being of greater probative value than opinions alone. MPEP §716.01(c) III. In this regard, expert opinions should at least be considered as “intermediate” probative value, but are nonetheless still considered evidence.

Expert opinions tied to legal issues are still evidence and entitled to a minimum amount of probative value. Even in cases where the applicant submitted their own declaration of what was obvious to them, “some weight ought to be given to a persuasively supported statement of one skilled in the art on what was not obvious to him.” *In re Lindell*, 385 F.2d 453, 456 155 USPQ 521, 524 (CCPA 1967) (emphasis added). Similarly, even if an applicant’s own declaration of what was obvious to them is not sufficient to rebut a §103 obviousness rejection, it

is nonetheless still considered “*evidence to be evaluated* along with the other evidence of record...” *In re Weber*, 341 F.2d 143, 147, 144 U.S.P.Q. 495, 499 (1965) (emphasis added).

In the instant case, the Examiner is characterizing the Natarajan Declaration as an opinion on an ultimate issue of law and thereby refusing to consider the Declaration as evidence. This is clearly erroneous given that the declaration is an expert opinion stating the expectations of those skilled in the art in ¶ 14-17, similar to the declarants in *Sullivan*. Moreover, Dr. Natarajan is a disinterested party, like the declarants in *Sullivan*. At a minimum, Dr. Natarajan’s declaration is entitled to greater probative value than those of the self-interested declarants in *Lindell* and *Weber*, where even those declarations were deemed to be evidence. Given the strong mandate for the PTO to consider evidence, the Examiner’s failure to meaningfully consider the Declaration is clearly erroneous.

Furthermore, the Natarajan Declaration is not an opinion on a legal issue. The legal issue is whether the claimed invention would have been obvious in light of the combination of the prior art set forth by the Examiner. The opinions stated therein relate to factual findings. For example, the Examiner continues to believe that Havemann *et al.* teaches “the scientific concept that mononuclear cells [which includes monocytes] may differentiate into endothelial cells via stimulation by or exposure to PTN.” Applicants have explained in previous Responses that Havemann *et al.* does not contain this alleged teaching. Applicants submitted the Natarajan Declaration as factual evidence to show that Havemann *et al.* does not teach the use of PTN to differentiate monocytes into endothelial cells. For example, ¶14 indicates that she would not conclude that PTN can differentiate monocytic cells into endothelial cells based on the Havemann *et al.* disclosures. The Examiner must consider this evidence.

Simply stated, the Examiner has misinterpreted Havemann *et al.* and refuses to believe that Havemann *et al.* does not teach one of ordinary skill in the art to use PTN to differentiate monocytes into endothelial cells, even when presented by a declaration from one of ordinary skill in the art indicating that Havemann *et al.* does not teach the use PTN to differentiate monocytes into endothelial cells. Instead, the Examiner dismisses the evidence and incorrectly classifies it as “Applicant’s opinion on the ultimate legal issue.”

Whether the Claims Exclude Further Steps That Include a Culture Condition Containing
Gangliosides, Phospholipids, and Glycolipids Is Not the Issue

Examiner's assertion that the claims' "comprising" language "do not exclude the use of gangliosides [sic], phospholipids, and glycolipids" ignores the claim language as a whole. Applicants wish to remind the Examiner that the claims are directed to artificially increasing the expression of pleiotrophin (PTN) in the monocytic cell by **transducing** the monocytic cell *in vitro* with a retrovirus expressing PTN such that the monocytic cell transdifferentiates into an endothelial cell. Applicants' claims are not directed to the use of culture conditions to induce transdifferentiation of the monocytic cell into the endothelial cell. Whether the claims exclude further steps that include a culture condition containing gangliosides, phospholipids, and glycolipids is not the issue; the Examiner is missing the point that the active step of transducing the monocytic cell *in vitro* with a retrovirus expressing PTN causes the monocytic cells to transdifferentiate into an endothelial cell. The application clearly shows that PTN transdifferentiates the monocytic cell into an endothelial cell. See e.g., specification, page 9, lines 14 to page 15, line 16.

The Examiner appears to allege that Souttou adds to the disclosure that PTN is responsible for transdifferentiating monocytic cells into endothelial cells by its disclosure that PTN is an angiogenic growth factor. The Examiner's rationale is flawed. Souttou's disclosure that PTN is an angiogenic growth factor does not render PTN as an obvious choice for use as a transdifferentiation factor with an expectation that PTN will successfully transdifferentiate a monocytic cell into an endothelial cell. The Examiner is adamant in his belief that Havemann "explicitly" discloses that PTN is a growth factor that promotes the differentiation of mononuclear cells into endothelial cells. Applicants have explained numerous times that Havemann *et al.* does not explicitly make this disclosure and that Havemann *et al.* does not enable this use. Applicants have shown that there are approximately 34 **billion** possible combinations of growth factors based on Havemann *et al.*'s disclosure. To determine which combination(s) of growth factor(s) will transdifferentiate a monocytic cell into an endothelial cell will require undue experimentation. Thus, Havemann *et al.* does not provide an enabling disclosure. The Natarajan Declaration was submitted as evidence to show that one of ordinary skill in the art would not find that Havemann *et al.* teaches the use of PTN to differentiate

monocytes into endothelial cells. As discussed above, the Examiner must consider the Natarajan Declaration because it contains opinions on the facts. Applicants respectfully request reconsideration in light of the arguments on record as well as the Natarajan Declaration.

Impermissible Hindsight Was Used by the Examiner

The Examiner insists that no impermissible hindsight was used. Applicants wish to point out that the Examiner's knowledge that **one** growth factor is responsible for transdifferentiation of a monocytic cell into an endothelial cell is gleaned from Applicants' disclosure. This feature is not disclosed by the prior art of record. The Examiner's erroneous assertion that simply testing 35 culture conditions, each with one growth factor, is necessarily based on Applicants' disclosure that PTN induces monocytic cells to transdifferentiate into endothelial cells. The prior art discloses the use of culture conditions, including **one or more** growth factors, to influence differentiation, survival, migration or vascularization. As discussed above, the list of growth factors provides one of ordinary skill in the art a pool to draw a myriad of possible combinations of growth factor(s) to induce transdifferentiation of the mononuclear cells into endothelial cells. As explained above, the number of possible combinations of growth factor(s) from a list of 35 growth factors is **34,359,738,367**.

In view of the foregoing, the combination of Havemann *et al.*, Souttou *et al.* and Powers *et al.* would not lead one of ordinary skill in the art to reasonably predict and expect that PTN would successfully transdifferentiate a monocytic cell into an endothelial. Accordingly, the claimed invention is not obvious. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim 3 is rejected under 35 U.S.C. §103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.* and Powers *et al.*, as applied to claims 1 and 11 *supra*, and in further view of Kume *et al.* for reasons of record. Applicants respectfully traverse this rejection.

Applicants submit that the combination of Havemann *et al.*, Souttou *et al.*, Powers *et al.* and Kume *et al.* would not render claim 3 obvious. For all the reasons discussed above, the combination of Havemann *et al.* Souttou *et al.* and Powers *et al.* would not render claim 1 obvious. Since claim 3 depends from claim 1, it would similarly not be obvious as the determination of obviousness of the claim also takes into account, among other things, the

predictability that a monocytic cell transduced with a retrovirus expressing PTN would transdifferentiate into an endothelial cell and the same reasonable expectation of success. Since there is no predictability and no reasonable expectation of success from the combination of the Havemann *et al.*, Souttou *et al.* and Powers *et al.* there will not be any predictability or reasonable expectation of success for the combination of Havemann *et al.* Souttou *et al.*, Powers *et al.* and Kume *et al.*; although Applicants do not concede that it is proper to combine Kume *et al.* with Havemann *et al.*, Souttou *et al.*, and Powers *et al.* In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection under §103(a).

Claim 4 is rejected under 35 U.S.C. §103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.*, Powers *et al.* and Kume *et al.*, as applied to claims 1, 3, and 11 *supra*, and in further view of Pufe *et al.*, Howett *et al.* and Eslami *et al.* for reasons of record. Applicants respectfully traverse this rejection.

Applicants again suspect and submit that Kume *et al.* was erroneously applied to the rejection of claim 4. The Examiner has applied Kume *et al.* to reject claim 3; however, claim 4 does not depend from claim 3. As such, Kume *et al.* does not appear to be applicable to claim 4. Applicants again request clarification regarding Kume *et al.* Nonetheless, Applicants submit that the combination of Havemann *et al.*, Souttou *et al.*, Powers *et al.*, Kume *et al.*, Pufe *et al.*, Howett *et al.* and Eslami *et al.* would not render claim 4 obvious. As discussed above, the combination of Havemann *et al.*, Souttou *et al.* and Powers *et al.* would not render claim 1 obvious. Since claim 4 depends from claim 1, it would similarly not be obvious as the determination of obviousness of the claim also requires, among other things, the predictability that a monocytic cell transduced with a retrovirus expressing PTN would transdifferentiate into an endothelial cell and the same reasonable expectation of success. Since there is no predictability and no reasonable expectation of success from the combination of Havemann *et al.*, Souttou *et al.*, and Powers *et al.*, there will not be any predictability or reasonable expectation of success for the combination of Havemann *et al.*, Souttou *et al.* Powers *et al.*, Kume *et al.*, Pufe *et al.*, Howett *et al.* and Eslami *et al.*; although Applicants do not concede that it is proper to combine Kume *et al.*, Pufe *et al.*, Howett *et al.* and Eslami *et al.* with Havemann *et al.*, Souttou *et al.*, and Powers *et al.* In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection under §103(a).

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.*, Powers *et al.*, Kume *et al.*, Pufe *et al.*, Howett *et al.* and Eslami *et al.* as applied to Claims 1, 3-4 and 11 *supra*, and in further view of Kawamoto *et al.* for reasons of record. Applicants respectfully traverse this rejection.

It appears the Examiner has mistakenly applied Kume *et al.*, Pufe *et al.*, and Howett *et al.* to claim 12 because claim 12 is only dependent on claim 1. Clarification from the Examiner is again requested. Regardless, Applicants submit that the combination of Havemann *et al.*, Souttou *et al.*, Powers *et al.*, Kume *et al.*, Pufe *et al.*, and Howett *et al.* does not render obvious the use of a retrovirus expressing PTN to induce differentiation of the monocytic cells into endothelial cells as discussed in detail above. Thus, the combination including Kawamoto *et al.* does not render it obvious to first transduce a retrovirus expressing PTN into the monocytic cell to induce differentiation into an endothelial cells and then allow the differentiation to occur *in vivo*. In light of the above, Applicants respectfully request reconsideration and withdrawal of this rejection under §103(a).

Claims 5, 13, 15, and 18 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.* and Powers *et al.* for reasons of record. Applicants respectfully traverse this rejection. While Applicants do not concede to the merits of the Examiner's rejection, claims 5, 13, 15, and 18 have been cancelled and thus this rejection is rendered moot. Applicants reserve the right to pursue the subject matter of these claims in one or more continuing applications.

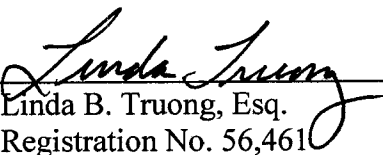
Claims 7 and 16 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.* and Powers *et al.*, as applied to claims 5, 13, 15, and 18 *supra*, and in further view of Kume *et al.* for reasons of record. Applicants respectfully traverse this rejection. While Applicants do not concede to the merits of the Examiner's rejection, claims 7 and 16 have been cancelled and thus this rejection is rendered moot. Applicants reserve the right to pursue the subject matter of these claims in one or more continuing applications.

Claims 8 and 17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.*, Powers *et al.*, and Kume *et al.* as applied to claims 5, 7, 13, 15-16, and 18 *supra*, and in further view of Pufe *et al.*, Howett *et al.*, and Eslami *et al.* for reasons of record. Applicants respectfully traverse this rejection. While Applicants do not concede to the merits of the Examiner's rejection, claims 8 and 17 have been cancelled and thus, this rejection is rendered moot. Applicants reserve the right to pursue the subject matter of these claims in one or more continuing applications.

Claim 19 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.*, Powers *et al.*, Kume *et al.*, Pufe *et al.*, Howett *et al.*, and Eslami *et al.*, as applied claims 5, 7-8, 13, and 15-18 *supra*, and in further view of Kawamoto *et al.* for reasons of record. Applicants respectfully traverse this rejection. While Applicants do not concede to the merits of the Examiner's rejection, claim 19 has been cancelled and thus, this rejection is rendered moot. Applicants reserve the right to pursue the subject matter of this claim in one or more continuing applications.

All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If for any reason Examiner finds the application other than in condition for allowance, Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (213) 633-6800 to discuss the steps necessary for placing the application in condition for allowance.

Respectfully submitted,
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